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## **VENOUS THROMBOEMBOLISM IN WOMEN**

### **RISK FACTORS AND LONG TERM FOLLOW-UP**

#### **AKADEMISK AVHANDLING**

som för avläggande av medicine doktorsexamen vid Karolinska  
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# ABSTRACT

## Background

Venous thromboembolism (VTE) is a common and potentially life threatening disease. Women have different risk factors than men at both first and recurrent VTE. The aim of this thesis was to further identify and explore risk factors for VTE in young and middle aged women.

## Methods

A nationwide case-control study of genetic and environmental risk factors for VTE in women aged 18-64 years was conducted in Sweden 2001-2009. The study was called Thrombo Embolism Hormone Study (TEHS) and comprised 1377 cases and 1402 age matched controls. In a sub study called hypo-TEHS, 244 of the cases included in the TEHS-study were followed up with plasma samples and questionnaires after cessation of anticoagulant therapy. Levels of coagulation factors and thrombin generation was measured and compared between obese and non obese patients. The women were also followed up at least 24 months after the diagnosis of VTE to assess data on recurrence. We investigated if there was any correlation between the levels of thrombin generation, resistance to activated protein C (APC) and increased risk of recurrent events. To assess the influence of other risk factors for recurrent VTE, all cases included in TEHS were followed up after four years in the TEHS-follow-up study.

## Results

Data from the TEHS study presented in this thesis showed that family history of VTE was predictive of increased risk of hormone, surgery and cast related VTE in women. In the hypo-TEHS study we found that obese women with VTE had increased levels of thrombin generation with two different laboratory methods, compared to the non obese women with VTE. Obesity was also related to higher inflammatory markers such as CRP and fibrinogen. Furthermore we found that increased thrombin generation was associated to increased risk of recurrent VTE, as was APC-resistance in the absence of the factor V Leiden mutation. In the TEHS follow-up study the risk of recurrence in women was found to be only 2 %. When the risk of recurrence in patients with hormone related first thrombosis was evaluated we found it to be higher than in surgery provoked first event but lower than in women with unprovoked first thrombosis.

## Conclusions

The most important risk factors for VTE in young and middle aged women are use of hormones, surgery and cast. Assessment of family history of venous thrombosis could help to better identify women at increased risk prior to hormonal treatment or decision on prophylaxis after surgery/ cast. Obesity is another important risk factor for both first and recurrent VTE. Obese female VTE patients had higher thrombin generation than non obese patients which could represent one mechanism of how obesity is related to the increased risk of recurrent VTE. In the clinical situation, the overall risk of recurrence in VTE must be weight against the risk of bleeding complications on anticoagulant therapy. Data from the hypo-TEHS study showed that women with APC-resistance in the absence of Factor V Leiden are at increased risk of recurrence. In the TEHS follow-up we fund the overall risk of recurrent VTE to be lower than the expected risk of bleeding complications. Integration of gender and knowledge on the specific risk factors in women when estimating the risk of recurrence could improve the care of VTE patients.